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Innovations in treatment of Vulvar Cancer

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SUMMARY

Invasive squamous cell carcinoma of the vulva is a rare disease and mainly affects elderly women. Seventy percent of the patients have early-stage disease without inguinofemoral lymph node metastases and have an excellent prognosis after surgery with a five-year survival of about 90%. However, the complication rate of the surgical treatment is high. Therefore, there is a trend toward less radical treatment. In this thesis, new diagnostic methods to detect inguinofemoral lymph node metastases other than by performing a complete inguinofemoral lymphadenectomy are presented. Moreover, different surgical options for the treatment of patients with squamous cell carcinoma and melanoma of the vulva are evaluated and discussed with respect to benefits and risks of these treatment policies.

In **Chapter 1** a review is given of current diagnostic methods for prediction of lymph node metastases and of different treatment options for patients with squamous cell carcinoma and melanoma of the vulva. Noninvasive methods to diagnose inguinofemoral lymph node metastases appear to be disappointing so far. Therefore, the further development of minimally invasive techniques, like the sentinel lymph node procedure, in vulvar cancer is warranted.

One of these non-invasive techniques to detect inguinofemoral lymph node metastases is L-[1-¹¹C]-tyrosine positron emission tomography (TYR-PET). **Chapter 2** describes the results of a study in which the role of TYR-PET in identification of inguinofemoral lymph node metastases of squamous cell carcinoma of the vulva was investigated in 25 patients. The results were compared with preoperative palpation of the groins and the histopathology. Neither palpation nor TYR-PET was able to adequately predict or, more important, exclude presence of inguinofemoral lymph node metastases. Two different methods of TYR-PET-scanning (“whole body scans” and “attenuation corrected static emission scans”) gave comparable results. Especially because of the high number of hot spots on the PET scans (7/25 patients) that were not confirmed to be lymph node metastases by histopathological examination, this method is considered as not appropriate in patients with squamous cell carcinoma of the vulva.

In **Chapter 3**, clinical characteristics of vulvar cancer are described and an overview is given of the literature on sentinel lymph node procedure in vulvar cancer.

In **Chapter 4** the feasibility of the sentinel lymph node procedure with the combined technique (preoperative lymphoscintigram with ^{99m}Tc-labeled nanocolloid and intraoperative patente blue) was studied in 10 patients with squamous cell carcinoma of the vulva with clinically negative groins. After the sentinel lymph node procedure,

complete uni- or bilateral inguino-femoral lymphadenectomy via separate incisions was performed in combination with wide local excision. The procedure was well tolerated. All sentinel lymph nodes were identified with the hand-held probe. Only 56% of the sentinel lymph nodes were blue. So identification of the sentinel lymph nodes in patients with squamous cell carcinoma of the vulva with the combined technique appeared to be feasible and superior to identification by patent blue only. Two of 10 patients had lymph node metastases, which were found at least in the sentinel lymph nodes. In the other 8 patients the sentinel and nonsentinel lymph nodes did not show metastatic disease. In these 10 patients histopathology of the sentinel lymph nodes was representative for the other lymph nodes. It was concluded that further development of this technique might be useful.

Chapter 5 describes in detail how to perform the sentinel lymph node procedure with the combined technique in patients with squamous cell carcinoma of the vulva. Attention is paid to selection of patients, preoperative care, equipment necessary for the sentinel lymph node procedure, how and where to inject the nanocolloid and patent blue and details of histopathological examination.

In **Chapter 6** the diagnostic accuracy of the sentinel lymph node procedure in patients with early-stage squamous cell carcinoma of the vulva was studied. Furthermore, the feasibility of performing step sectioning and immunohistochemistry for detection of metastatic disease in sentinel lymph nodes, was evaluated. A total number of 59 patients underwent sentinel lymph node procedure with the combined technique. Subsequently complete uni- or bilateral inguino-femoral lymphadenectomy was performed in combination with wide local excision. In 59 patients 107 inguino-femoral lymphadenectomies were performed (11 unilateral and 48 bilateral). All sentinel lymph nodes, as observed on preoperative lymphoscintigram, were identified successfully intraoperatively. Routine histopathological examination showed lymph node metastases in 27 groins, that were all detected by the sentinel lymph node procedure. The negative predictive value for a negative sentinel lymph node was 100% (97.5% CI: 95-100%). Step sectioning and immunohistochemistry were performed in all sentinel lymph nodes, which were negative at routine histopathological examination. Four additional metastases in 102 (4% (95% CI: 1-9%)) sentinel lymph nodes were found. Apparently sentinel lymph node procedure with the combined technique is highly accurate in predicting the inguino-femoral lymph node status in patients with early-stage vulvar cancer.

The aim of the study in **Chapter 7** was to assess the opinion on the acceptable false-negative rate of the sentinel lymph node procedure in patients with vulvar cancer, who in the past underwent standard routine radical vulvectomy and complete inguino-femoral lymphadenectomy (and frequently experienced the complications), and in gynecologists treating patients with vulvar cancer. Structured questionnaires were sent to both patients and gynecologists. The patients were treated for vulvar cancer between 1985 and 1993,

and they are all in complete remission with median follow-up of 118 months (range: 76-185). Questions to the patients handled with experienced side effects of the standard treatment and the opinion on the acceptable false-negative rate of the sentinel lymph node procedure. Response rate among patients was 91% (106/117). Forty percent of the patients experienced one or more infections in the legs (cellulitis) and 47% of the patients still experience either severe pain and/or severe lymph edema in the legs. Sixty-six percent of the patients preferred complete inguinofemoral lymphadenectomy in case of a false-negative rate of the sentinel lymph node procedure of 5%. Their preference was not related to age or experienced side effects. Response rate among gynecologists was 80% (80/100) of whom 60% of them were willing to accept a 5-20% false-negative rate of the sentinel lymph node procedure. While gynecologists may consider the sentinel lymph node procedure a promising diagnostic tool, the majority of vulvar cancer patients, who underwent complete inguinofemoral lymphadenectomy in the past and frequently experienced the complications, would not advise introduction of this technique because they hardly want to take any risk of missing a lymph node metastasis. In order to continue the clinical implementation of the sentinel node procedure without ignoring the opinion of the majority of patients, doctors will have to convince future vulvar cancer patients, that for each individual patient, the benefits of the sentinel node procedure far outweigh any possible limited risks.

In **Chapter 8** a patient is presented with a local recurrence of vulvar cancer after primary treatment. In the past she underwent wide local excision and unilateral inguinofemoral lymphadenectomy. She also received postoperative radiotherapy on both groins because of two lymph node metastases. Sentinel lymph node procedure was performed to investigate how surgery and/or radiotherapy had influenced lymph drainage patterns. Our preliminary experience shows that the sentinel node procedure is feasible in patients with locally recurrent vulvar cancer. However, extension of this experience should learn us whether or not future patients with a local recurrence may benefit of the application of the sentinel node technique.

In **Chapter 9** an overview is given of patients with vulvar melanoma, treated between 1978 and 2000 at the Groningen University Hospital. The aim of the study was to analyze treatment and follow-up of 33 patients with vulvar melanoma and to report the first experience with the sentinel lymph node procedure in nine patients. From 1997, sentinel lymph node procedure with the combined technique (^{99m}Tc labeled Nanocolloid and Patente Blue-V) was performed as a standard staging procedure for patients with vulvar melanoma with thickness > 1mm and no clinically suspicious inguinofemoral lymph nodes. For the present study clinicopathological data of all 33 patients with vulvar melanoma, treated between 1978 and 2000 in our hospital, were reviewed and analyzed. Identification of sentinel lymph nodes was successful in all nine patients, who were referred for treatment of vulvar melanoma. Three patients underwent subsequent

complete inguinofemoral lymphadenectomy because of metastatic sentinel lymph nodes. In follow-up groin recurrences (in-transit metastases) occurred in two of these nine patients, both 12 months after primary treatment. Both patients had melanomas with thickness > 4 mm and previously a negative sentinel lymph node. There was a trend towards more frequent groin recurrences in patients after sentinel lymph node procedure (2/9) when compared to our 24 historic controls (0/24) ($p=0.06$). Of all 33 patients, five patients developed local recurrences, two patients groin recurrences and 11 patients distant metastases. Twelve patients died of vulvar melanoma. Seventeen patients with a median follow-up of 66 months (range 9-123) are presently alive (overall survival:52%). Although numbers are small, our study shows that the sentinel lymph node procedure is able to identify patients, who have occult lymph node metastases and who may benefit from lymphadenectomy for locoregional control and prevention of distant metastases. However, simultaneously our data suggest that the sentinel lymph node procedure may increase the risk on locoregional recurrences (in-transit metastases), especially in patients with thick melanomas. The potential role of sentinel lymph node procedure as an alternative method of nodal staging in patients with vulvar melanoma needs further investigations only within the protection of clinical trials and should probably restricted to patients with melanomas with intermediate thickness (1-4 mm).

The aim of the study, presented in **Chapter 10**, was to determine whether modifications in treatment of vulvar cancer patients influence the recurrence rate and survival. Between 1982 and 1998, 253 patients with T1 and T2 invasive squamous cell carcinoma of the vulva were treated by essentially the same team of gynecologic oncologists: 168 patients (group I) underwent radical vulvectomy with “en bloc” inguinofemoral lymphadenectomy as standard therapy, while since 1993, standard therapy in 85 patients (group II) was changed into wide local excision (with intentional macroscopic margins of 1 cm) with uni- or bilateral inguinofemoral lymphadenectomy via separate incisions. Histopathological parameters were reviewed. Recurrence rate and survival were compared between both groups. In group II, sections of the specimen were taken such that the exact basal and lateral margins could be determined prospectively. No differences were found between both groups with respect to age and histopathological parameters. Median follow-up was 110 months (range: 3-220). In group II the overall recurrence rate (33.3%) within four years was increased compared to group I (19.9%) ($p=0.03$). In group II, 5/79 (6.3%) of the patients developed fatal groin or skin bridge recurrences compared to 2/159 (1.3%) in group I ($p=0.029$), not resulting in differences in overall survival. Within group II, no patients with tumor-free margins 8 mm (0/40) developed local recurrences, while 9/39 patients with margins \leq 8 mm developed local recurrences ($p=0.002$). This study shows that the overall recurrence rate in vulvar cancer patients is increased with wide local excision and inguinofemoral lymphadenectomy via separate incisions compared with the “en bloc” approach. Fatal recurrences in either groin or skin bridge were more frequent in patients in group II (5/79=6.3%) than in group I (2/159=1.3%), but, probably due to lack of power, this did

not result in shorter overall survival. In spite of the intentional macroscopic margins of 1 cm, in 50% of the patients microscopic margins were ≤ 8 mm, resulting in an increased risk on local recurrences. Based on these data, it was recommended to obtain macroscopic margins of 2 cm at local treatment of vulvar cancer patients.

GENERAL CONCLUSIONS AND FUTURE PERSPECTIVES

Literature and contents of this thesis show that there are no clinical, pathological or non-invasive methods available which accurately exclude inguinofemoral lymph node metastases in patients with squamous cell carcinoma of the vulva.

Sentinel lymph node procedure and clinical implementation

The sentinel lymph node procedure appears to be a promising new diagnostic tool to predict the lymph node status with a very high negative predictive value of a negative sentinel lymph node. Due to the low incidence of squamous cell carcinoma of the vulva, there are no data yet about the safety of omitting inguinofemoral lymphadenectomy in case of a negative sentinel node. To speculate on the future role of the sentinel lymph node procedure in vulvar cancer patients it is useful, to consider the present role in cutaneous melanoma and breast cancer: two malignancies with a higher incidence and therefore more experience with the sentinel lymph node procedure.

For years, the role of elective lymphadenectomy in patients with cutaneous melanoma with invasion > 1 mm, has been an issue among surgeons. Four randomized trials have failed to demonstrate any survival advantage after elective regional lymphadenectomy.¹ Therefore, the sentinel lymph node procedure was considered as an interesting alternative for nodal staging. Essner et al showed no difference in survival between elective lymphadenectomy and sentinel lymph node procedure² while Clary et al found a higher proportion of nodal recurrences in patients with a negative sentinel node compared to patients without lymph node metastases at elective inguinofemoral lymphadenectomy.³ So far, while the diagnostic utility of the sentinel lymph node procedure has been well established now, its therapeutic value and safety remain unproven in cutaneous melanoma. In spite of this, in many centers sentinel lymph node procedure is already part of the standard treatment for these patients. To evaluate the possible benefit of the sentinel lymph node procedure, the multicenter Selective Lymphadenectomy Trial (MSLT) was initiated by Morton.⁴ In this phase III study, patients with cutaneous melanoma ≥ 1 mm thick and/or \geq Clark Level IV are randomized between only wide local excision or wide local excision with sentinel lymph node procedure. Only in case of a positive sentinel lymph node, complete lymphadenectomy will be performed.⁴ Results of this "Morton-trial" will be awaited.

Also in breast cancer, the sentinel lymph node concept has developed quite extensively the last 10 years. The high diagnostic accuracy of the sentinel node in predicting the lymph node status in the axilla was reported in different studies. Giuliano observed 67 patients with a negative sentinel lymph node and found no local or axillary recurrences.⁵ In patients with a positive sentinel node it is not clear yet whether further axillary staging gives survival advantage. There may be a role for postoperative radiotherapy, possibly with chemotherapy, instead of a complete lymphadenectomy. At present there are two study groups in the USA who investigate several important issues with respect to the safety, morbidity and survival of the sentinel lymph node procedure, complete lymphadenectomy and radiotherapy in breast cancer patients.⁶ The AMAROS trial (After Mapping of the Axilla Radiotherapy Or Surgery) is an EORTC protocol in which patients with a positive sentinel node are randomized between complete axillary dissection and radiotherapy.

In order to further explore the application of the sentinel lymph node procedure in vulvar cancer currently a so-called two-step randomized multicenter study has been designed: in step I participating centers need to perform sentinel lymph node procedures with subsequent complete inguinofemoral lymphadenectomy in 10 patients as part of the learning curve. When a center has successfully completed step I, subsequent patients with a negative sentinel lymph node will be randomized between complete inguinofemoral lymphadenectomy and observation in step II. Primary endpoints in this study will be 1) to show equivalence for groin recurrences in the two arms and 2) improved quality of life in the observational arm. A major drawback of such a study design is the large number of patients with vulvar cancer needed ($n =$ approximately 700).

Awaiting the start of this randomized trial, an observational multicenter study with stopping rules has been initiated. Centers are allowed to participate when the learning curve has been finished. Only in case of a positive sentinel lymph node, complete inguinofemoral lymphadenectomy is performed. Patients with negative sentinel lymph node(s) are observed every two months. Another option is to give postoperative radiotherapy instead of complete inguinofemoral lymphadenectomy in case of a positive sentinel lymph node. This will be an interesting subject of future study.

Concerning further study in patients with melanoma of the vulva, there is a huge problem with respect to the extremely low incidence of vulvar melanoma. In the light of the two groin recurrences after negative sentinel lymph node (in-transit metastasis) and the node recurrences after negative sentinel node in cutaneous melanoma as reported in literature, a multicenter-observational study should be started in patients with vulvar melanoma, to find out whether there is any place for the sentinel lymph node procedure in patients with vulvar melanoma with thickness intermediate thickness.

Histopathology

Besides the uncertainty about the safety of the sentinel lymph node procedure, the role of additional histopathological techniques is another issue and subject of different studies. There are several methods for intraoperative and postoperative evaluation of the sentinel lymph nodes, often without enough knowledge about the clinical consequences of these findings.⁷

Intraoperative techniques such as frozen sections, have the great advantage that a complete lymphadenectomy, when necessary, can be performed in the same operating sessions and may prevent a second operation. In general, the sensitivity of the frozen section, which is mostly a single haematoxylin/eosin (H&E) section, is 80%. These patients with a positive sentinel lymph node at frozen section, can undergo an immediate lymphadenectomy which is an obvious advantage. Therefore we recommend the use of frozen sections in the sentinel lymph node procedure. The results of intraoperative imprint cytology are comparable with frozen section.

Step sectioning is a postoperative technique to evaluate sentinel lymph nodes. Various protocols have been used for this technique, mostly in combination with immunohistochemistry. Both techniques are very time-consuming. A compromise should be found between sensitivity and workload. Van Diest et al recommend to cut additional pairs of sections of sentinel lymph nodes after lamellating sentinel lymph nodes into pieces of 0.5 cm: 5 steps with 250 μ interval, one section is stained with H/E and another section is immunostained with cytokeratin 1% AE1/AE3 antikeratin.

There is little experience with flow cytometry, while RT-PCR is the most sensitive method for detection of metastases in sentinel lymph nodes so far and will increase the number of metastases with more than 25%. The clinical consequence has still to be investigated in different types of tumors. Until now there are no data about flow cytometry and RT-PCR in vulvar cancer.

Another technique which should be considered is the ultrasound-guided fine-needle aspiration before the planned treatment. In case of a lymph node metastasis, immediate complete inguinofemoral lymphadenectomy can be performed, instead of a sentinel lymph node procedure.⁸

The lack of knowledge about the clinical value of additional histopathological techniques leads to the necessity to include these techniques into trials on sentinel lymph node procedure. The role of frozen section, step sectioning and immunohistochemistry is investigated in the observational sentinel lymph node study on vulvar cancer.

The use of additional histopathological techniques has led to stage migration. Tjan-Heijnen et al reviewed literature to investigate the role of micrometastases for prognosis in breast cancer patients.⁹ The background was that micrometastases will lead to stage migration to higher stages, which will lead to more adjuvant treatment. They found that only one of eight studies concluded that occult lymph node metastases were an independent risk factor for reduced survival. The outcome was dependent on the size of the nodal metastasis. They proposed to classify small micrometastases < 0.5 mm in a

separate N1a stage to prevent stage migration. These patients will get the same treatment as patients with N0, for the prognostic relevance of micrometastases has not been proven yet and the value of adjuvant therapy can be questioned for patients with otherwise good prognostic factors.

Treatment Modifications

Wide local excision and inguinofemoral lymphadenectomy via separate incisions is nowadays generally accepted as standard treatment for patients with early-stage vulvar. A higher risk on groin and skin bridge recurrences is reported after the replacement of the radical approach by wide local excision and inguinofemoral lymphadenectomy via separate incisions. In our hands all patients with regional recurrences died of disease. Moreover, 50% of the patients had histological margins of ≤ 8 mm (in spite of surgical margins of 1 cm) leading to a higher local recurrence rate. In the light of the extensive morbidity of the radical approach, it is our opinion that gynecologic oncologists should continue with the use of separate incisions, but our recommendation is to aim at surgical free margins of 2 cm. While inguinofemoral lymphadenectomy via separate incisions remains part of the standard treatment, hopefully, in the future, 80% of the inguinofemoral lymphadenectomies will be replaced by removal of only one or two (negative) sentinel lymph nodes

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